REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

Status of Claims

Claims 1, 3 and 18 are currently pending in the application, with claims 1 and 18 being the independent claims. Claim 21 is canceled without prejudice to or disclaimer of the subject matter therein. Claims 2, 4-17 and 19-20 were previously canceled.

Claims 1, 3 and 18 are amended to specify that the methods of the invention comprise administering an elastase inhibiting agent that inhibits elastase activity within the cells. Support for the amendment to claims 1, 3 and 18 may be found throughout the specification as originally filed, including paragraphs [0001], [0007]-[0008] and Figure 4, showing that the elastase inhibitor enters into the intact cells and inhibits the elastase enzyme which is activated during necrosis in the cells. Further, claim 1 is amended to specify that the subject is affected by Parkinson's Disease. Support for the amendment to claim 1 may be found throughout the specification, including paragraphs [0020] (*see* neurodegenerative disorders). Finally, claims 3 and 18 are amended to correct antecedent basis and for formal matter.

These amendments do not introduce any new matter into the application and their entry is respectfully requested.

The Telephonic Interview with the Examiner

Applicants wish to thank Examiner Niebauer for the courtesy extended to Applicants' representative during the telephonic interview of October 27, 2010. The foregoing amendments and the following remarks reflect the issues discussed and agreed upon during the interview.

The Objection to the Specification

The Office Action, at pages 3-5, objects to the amendments to the specification filed December 19, 2009, as allegedly introducing new matter into the disclosure. Applicants respectfully traverse this ground of objection.

Nevertheless, solely in the interest of advancing prosecution, the foregoing amends the specification to the original wording. Thus, the objection is moot. Reconsideration and withdrawal of this ground of objection are therefore respectfully requested.

The Information Disclosure Statement

The Office Action, at page 5, states that no IDS was submitted within a week of December 19, 2009. In response, Applicants submit an IDS herewith. The Examiner is kindly requested to consider the references cited in the IDS.

CLAIM REJECTIONS

35 U.S.C. § 112 Rejections

The Rejection Under 35 U.S.C. § 112, Second Paragraph

The Office Action, at pages 5-6, rejects claim 3 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner contends that the sentence "the one or more elastase inhibiting agents" in claim 3 lacks antecedent basis. Applicants respectfully traverse this ground of rejection.

Nevertheless, solely in the interest of expediting prosecution, the foregoing amends claim 3 to delete the phrase "one or more". Thus, the rejection is moot. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

The Rejection Under 35 U.S.C. § 112, First Paragraph

The Office Action, at pages 6-7, rejects claims 18 and 21 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner contends that the phrase "wherein said amount of elastase inhibiting agent is less than the optimal amount for inhibiting necrosis when an anti-apoptotic agent is not used" in claim 18, and the phrase "wherein said elastase inhibiting agent is capable of entering said cells and inhibiting an enzyme acting in the cells undergoing necrosis" in claim 21 lack support in the specification. Applicants respectfully traverse this ground of rejection.

Nevertheless, solely in the interest of expediting prosecution, the foregoing cancels claim 21 and amends claim 18 to delete the phrases in question. Thus, the rejection is moot. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

35 U.S.C. § 102 Rejections

The Office Action, at pages 8-11, rejects claims 1 and 21 under 35 U.S.C. § 102(b), as allegedly being anticipated by US Patent No. 6,001,813 to Gyorkos et al. ("Gyorkos"). Applicants respectfully traverse this ground of rejection.

1. Summary of the Claimed Invention

The presently claimed invention is drawn to a method for ***inhibiting necrosis*** of ***neuronal, Purkinje, hippocampal, pyramidal or glial cells*** in a ***subject affected by Parkinson's Disease,*** comprising administering an elastase inhibiting agent that inhibits elastase activity ***within the cells*** in an amount sufficient to inhibit necrosis of ***neuronal, Purkinje, hippocampal, pyramidal or glial cells***.

2. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

Gyorkos discloses inhibitors of the serine protease *human neutrophil elastase* (HNE) and provides a method of inhibiting a human neutrophil elastase comprising administering to a host in need of inhibition *methyloxycarbonyl-L-valyl-N-[1-(2-[5-(α,α-dimethylbenzyl)oxadiazolyl]carbonyl)-2-(S)-methylpropyl]-L-prolinamide*. Gyorkos fails to teach or suggest several essential elements of the claimed invention.

First, Gyorkos fails to teach a method for *inhibiting necrosis*, let alone a method for *inhibiting necrosis of neuronal, Purkinje, hippocampal, pyramidal or glial cells*, as claimed in the present application. Rather, Gyorkos provides a method for inhibiting human elastase which is active in *neutrophils*. Neutrophils are **not** neuronal, Purkinje, hippocampal, pyramidal or glial cells and do not undergo necrosis!

Necrosis is the irreversible and premature death of living tissue and cells. Applicants wish to point out that neurons are found in the nervous system, mainly in the central nervous system in vertebrates, and are characterized by electrical excitability and the presence of synapses. Purkinje cells are very large neurons located in the cerebellum. Hippocampal cells are located in the medial temporal lobe of the brain. Pyramidal cells are neurons found in several areas of the brain, including the cerebral cortex, the hippocampus and the amygdala. The glial cells surround the neurons in the brain. Neuron necrosis leads to brain death. **In contrast**, *neutrophils are white blood cells* and play a role as part of the immune system during acute inflammation. Neutrophils are removed by apoptosis, followed by phagocytosis by macrophages. Neutrophils are not involved in the necrosis of brain neuronal cells. In fact, under normal physiological conditions, **neutrophils do not undergo necrosis**.

Thus, Gyorkos fails to disclose a method for inhibiting necrosis of neuronal, Purkinje, hippocampal, pyramidal or glial cells undergoing necrosis, as claimed in the present application.

Second, Gyorkos fails to disclose a method comprising administering an elastase inhibiting agent that inhibits elastase activity ***within the cells***, as claimed in the present application. Rather, Gyorkos discloses a human neutrophil elastase (HNE) which "is a proteolytic enzyme *secreted* by polymorphonuclear leukocytes (PMNs) in response to a variety of inflammatory stimuli" (*see* col. 1, lines 23-26), and teaches that "this release of HNE and its ***extracellular proteolytic activity*** are *highly regulated and are normal, beneficial functions of PMNs*" (*see* col. 1, lines 26-28). An HNE which is (a) released by leukocytes; (b) has extracellular proteolytic activity; and (c) whose release and extracellular proteolytic activity are highly regulated and normal, beneficial functions of PMNs, as the one disclosed by Gyorkos, is **not** an *intracellular* elastase involved in *neuron necrosis* because the human neutrophil elastase (1) is secreted by neutrophils and thus is not active inside neuron cells; (2) has extracellular proteolytic activity and thus is not an intracellular elastase; and (3) its activity is highly regulated and has normal, beneficial functions, and thus is not involved in unregulated, harmful necrosis of neuronal cells. Accordingly, Gyorkos fails to teach an intracellular elastase inhibitor that inhibits necrosis in neuronal cells.

Third, Gyorkos fails to disclose an elastase inhibiting agent that inhibits *necrosis of neurons*. Gyorkos discloses an inhibitor of a human elastase which is active in neutrophils (HNE). As stated above, ***neutrophils are not involved in the necrosis of brain neuronal cells*** and, under normal physiological conditions, ***neutrophils do not undergo necrosis***. Furthermore, ***neutrophils are not involved in diseases associated with neuron necrosis, such as Alzheimer's Disease***. *See* Heneka and O'Banion 2010. *J. Neural Transm. 117*: 919-947, attached herewith as Exhibit A, in particular page 929, left column: "*In contrast, no convincing evidence exists for blood brain barrier disruption or significant leukocyte infiltration in the AD brain.*" *See* also Table 2 in Zipp and Aktas 2006 *TRENDS in Neurosciences 29*: 519-527, attached herewith as Exhibit B. Table 2 in Exhibit B clearly shows lack of neutrophil involvement in Alzheimer's Disease.

Fourth, Gyorkos fails to disclose administering an elastase inhibiting agent to a subject affected by Parkinson's Disease.

Thus, at least for the reasons stated above, Gyorkos fails to teach each and every element of the claimed invention and the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

35 U.S.C. § 103 Rejections

The Rejection of Claims 1 and 21

The Office Action, at pages 11-15, rejects claims 1 and 21 under 35 U.S.C. § 103(a) as allegedly being unpatentable over US Patent No. 6,001,813 to Gyorkos *et al.* ("Gyorkos") and Stein *et al.* 1986. *Biochemistry 25*: 5414-5419 ("Stein"). Applicants respectfully traverse this ground of rejection.

A. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

As demonstrated above, Gyorkos fails to teach or suggest several essential elements of the claimed invention.

First, Gyorkos fails to teach a method for *inhibiting necrosis*, let alone a method for *inhibiting necrosis of neuronal, Purkinje, hippocampal, pyramidal or glial cells*, as claimed in the present application. Rather, Gyorkos provides a method for inhibiting human elastase which is active in *neutrophils*. Neutrophils (a) are **not** neuronal, Purkinje, hippocampal, pyramidal or glial cells; (b) are not involved in the necrosis of brain neuronal cells; and (c) do not undergo necrosis.

Second, Gyorkos fails to disclose an elastase inhibiting agent that inhibits elastase activity ***within the cells***, as claimed in the present application. The human neutrophil elastase (HNE) disclosed by Gyorkos is (a) released by leukocytes and is not active inside neurons; (b) has extracellular proteolytic activity, not intracellular activity; and (c) has highly regulated activity and normal, beneficial functions, and is not involved in unregulated, harmful necrosis of neuronal cells.

Third, Gyorkos fails to disclose an elastase inhibiting agent that inhibits *necrosis of neurons*. Gyorkos discloses an inhibitor of human elastase which is active in neutrophils (HNE). Neutrophils are not involved in the necrosis of brain neuronal cells and do not undergo necrosis.

Fourth, Gyorkos fails to disclose administering an elastase inhibiting agent to a subject affected by Parkinson's Disease.

Thus, at least for the reasons stated above, Gyorkos fails to teach each and every element of the claimed invention. Stein does not remedy the deficiencies of Gyorkos described above.

Although Stein discloses elastase inhibitor III, the reference fails to teach or suggest a method for inhibiting necrosis of neuronal, Purkinje, hippocampal, pyramidal or glial cells in a subject, comprising administering an elastase inhibiting agent to the subject.

Thus, at least for the reasons stated above, the cited references, whether taken alone or in combination, fail to teach each and every element of the claimed invention.

B. Gyorkos Teaches Away from the Claimed Invention

Gyorkos teaches that the class of enzymes known as serine proteases may be segregated into three subclasses: elastases, chymases and tryptases, based on the differences in the P_1 residues, which define the enzyme specificity. Although Gyorkos provides the general disclosure that human neutrophil elastase-mediated processes are implicated in numerous conditions, including Alzheimer's disease, the reference clearly states that propyl endopeptidase does not fall into one of these categories and teaches that it is this enzyme, propyl endopeptidase, and **not** human neutrophil elastase, that has been implicated in the progression of memory loss in Alzheimer's patients (*see* paragraph bridging columns 3-4). Accordingly, Gyorkos does not teach that elastases are involved in neurodegenerative disorders, as the Examiner improperly contends. Quite to the contrary, Gyorkos clearly teaches that HNE mediated conditions are acute respiratory distress syndrome and ischemia/reperfusion (*see* column 4, lines 32-46), and nowhere does the reference disclose or suggest that elastases are involved in necrosis. Thus Gyorkos teaches away from the present invention, which provides the surprising and unexpected disclosure that cell necrosis is inhibited by an agent that inhibits elastase activity within the cells.

C. The Examples in the Specification Provide Unexpected Results

The examples in the specification clearly demonstrate that (a) elastase activity is induced during cell necrosis (*see* Figures 2, 3 and 4 and paragraphs [0066-0069]; (b) addition of elastase inhibitor to intact cells inhibits necrosis-activated elastase activity in the cells undergoing necrosis (*see* Figure 4 and paragraphs [0070, 0071] (c) different elastase inhibitors, i.e., a peptidic inhibitor, elastase inhibitor III, and a heterocyclic inhibitor (cortech), significantly inhibit necrosis (*see* Figures 5, 6, 7b, 10A, 11 and 12 and paragraphs [0072-0077] and [0082-0087]); (d) elastase inhibitors that do not penetrate into the cells have no effect on necrosis (*see* Figure 7C and paragraph [0077]); and (e) elastase inhibitor at concentration lower than the concentration that completely abrogates necrosis reduces necrotic cell death and partially shifts necrotic cell death to apoptotic cell death (see Figure 10B as compared to Figure 10A) and paragraphs[0082]-[0083].

These surprising and unexpected results provide evidence for the first time that necrosis, which is the irreversible and premature death of living tissue and cells, is significantly inhibited and/or shifted into apoptosis, which is programmed cell death. The invention of the present application has remarkable therapeutic implications, as it provides the means to prevent extensive and

irreversible tissue damage caused by necrosis by abrogating necrosis and treat damaged tissue by shifting necrotic cell death into natural apoptotic cell death. Accordingly, the invention is novel and non-obvious over the prior art.

D. There is no Reason to Combine the Elements in the Fashion Claimed

The Office Action, at pages 13-14, contends the following:

> One of skill in the art would have been motivated to substitute the chloromethyl ketone peptide disclosed by Stein for the tripeptide disclosed by Gyorkos because both are known elastase inhibitors and Stein teach that the peptide derived chloromethyl ketones have desired qualities such as being irreversible inhibitors of serine proteases (elastase is a serine protease). As such one would be motivated to treat the patient population of Gyorkos (those with Alzheimer's) using the peptide of Stein. One would have had a reasonable expectation of success since the peptides used are known elastase inhibitors.

Applicant asserts that the Examiner's allegations find no support in the cited references and are improper for several reasons.

First, neither Gyorkos nor Stein disclose or suggest a method for inhibiting necrosis, let alone a method for inhibiting necrosis of neurons, as claimed in the present application. Quite to the contrary! As stated above, Gyorkos teaches that **not** elastases, but rather propyl endopeptidase, has been implicated in the progression of memory loss in Alzheimer's patients (*see* column 4, lines 1-7). Thus, the artisan skilled in the art would have not been motivated to use an elastase inhibitor to inhibit cell necrosis because (a) neither Gyorkos nor Stein teach or suggest a method for inhibiting cell necrosis; and (b) because the cited prior art teaches that not elastases but propyl endopeptidase is involved in degenerative disorders.

Second, the Examiner's allegation that it would be obvious to substitute the tripeptide disclosed by Gyorkos with the chloromethyl ketone disclosed by Stein is improper because it is not based on the teachings of the prior art. Applicants point out that Gyorkos teaches that the inhibitory compounds of the invention are (a) potent inhibitors; (b) reversible inhibitors that form a transition state intermediate with the active site serine residue; (c) have high selectivity with respect to HNE; and (d) have stability regarding physiological conditions (*see* column 2, line 65, to column 3, line 8). Why, then, would the artisan skilled in the art substitute the beneficial, HNE-specific and reversible inhibitory compounds disclosed by Gyorkos with irreversible chloromethy ketone inhibitors as those disclosed by Stein, when Gyorkos teaches that the compounds of the invention are potent inhibitors of

human neutrophil elastase (HNE)? There would have been no motivation to make such a change, nor any reasonable expectation of success!

It is asserted that nothing in the combination of Gyorkos and Stein would lead the artisan skilled in the art to construe the claimed invention. Thus, the Office's allegation of obviousness is impermissible. For at least all the reasons stated above, the rejection of claims 1 and 21 under 35 U.S.C. § 103(a) is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

The Rejection of Claims 1, 3, 18 and 21

The Office Action, at pages 15-19, rejects claims 1, 3, 18 and 21 under 35 U.S.C. § 103(a) as allegedly being unpatentable over US Patent No. 6,001,813 to Gyorkos *et al.* ("Gyorkos") and Rohn *et al.* 2001. *American Journal of Pathology 158*: 189-198 ("Rohn"). Applicants respectfully traverse this ground of rejection.

1. Summary of the Claimed Invention

As stated above, the presently claimed invention is drawn to a method for inhibiting necrosis of neuronal, Purkinje, hippocampal, pyramidal or glial cells in a subject affected by Parkinson's Disease, comprising administering to the subject an elastase inhibiting agent that inhibits elastase activity ***within the cells*** in an amount sufficient to inhibit necrosis of the cells.

Further, the presently claimed invention is directed to a method for treating cell necrosis in a subject in need thereof, comprising administering to the subject one or more elastase inhibiting agents that inhibit elastase activity ***within the cells*** *in an amount sufficient to inhibit necrosis and cause partial conversion of necrosis to apoptosis*, and further administering an anti-apoptotic agent.

2. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

The deficiencies of Gyorkos have been demonstrated above. In addition, with regard to claims 3 and 18, Applicant wishes to point out that Gyorkos fails to teach two more essential elements of the claimed invention. First, Gyorkos fails to disclose administering an elastase inhibiting agent in an amount sufficient to cause partial conversion of necrosis to apoptosis. Quite to the contrary, nowhere does Gyorkos mention necrosis or apoptosis. Second, Gyorkos fails to disclose co-administration of an elastase inhibiting agent with an anti-apoptotic agent.

Rohn does not remedy the deficiencies of Gyorkos described above. Rohn only provides the general teachings that apoptosis mechanisms undergo activation in the neurons of AD brain. Like Gyorkos, Rohn fails to disclose or suggest a method for inhibiting necrosis of neuronal, Purkinje,

hippocampal, pyramidal or glial cells in a subject affected by Parkinson's Disease, comprising administering to the subject an elastase inhibiting agent that inhibits elastase activity within the cells in an amount sufficient to inhibit necrosis of the cells. Nowhere does Rohn teach that administration of elastase inhibitors in certain amounts cause partial conversion of necrosis to apoptosis. Furthermore, Rohn fails to disclose or suggest co-administering an elastase inhibiting agent and an anti-apoptotic agent, as claimed in the present application.

Thus, the cited prior art, whether taken alone or in combination, fails to teach each and every element of the claimed invention.

3. The Cited Prior Art Teaches Away from the Claimed Invention

As demonstrated above, Gyorkos teaches away from the present invention, because, contrary to the Examiner's improper allegation, the reference teaches that **not** neutrophil elastases which reside specifically in neutrophils, but rather propyl endopeptidase, has been implicated in the progression of memory loss in Alzheimer's patients (*see* column 4, lines 1-7), and nowhere does the reference disclose or suggest that elastases are involved in necrosis.

Rohn does not remedy the deficiencies of Gyorkos. Quite to the contrary, Rohn clearly teaches that neurofibrillary tangle formation (NTF) in Alzheimer's disease (AD) and activation of apoptotic mechanisms are two independent processes and NFT may serve as one stimulus, but it is not the only stimulus promoting the activation of apoptotic pathways (*see* Discussion). Thus, the cited prior art teaches away from the present invention, which provides the surprising and unexpected discovery that elastase inhibiting agents inhibit necrosis and, when administered in low doses, cause the partial conversion of nectrosis into apoptosis.

4. The Examples in the Specification Provide Unexpected Results

As stated above, the examples in the specification clearly demonstrate that (a) elastase activity is induced during cell necrosis (*see* Figures 2, 3 and 4 and paragraphs [0066-0069]; (b) addition of elastase inhibitor to intact cells inhibits necrosis-activated elastase activity in the cells undergoing necrosis (*see* Figure 4 and paragraphs [0070, 0071] (c) different elastase inhibitors, i.e., a peptidic inhibitor, elastase inhibitor III, and a heterocyclic inhibitor (cortech), significantly inhibit necrosis (*see* Figures 5, 6, 7b, 10A, 11 and 12 and paragraphs [0072-0077] and [0082-0087]); (d) elastase inhibitors that do not penetrate into the cells have no effect on necrosis (*see* Figure 7C and paragraph [0077]); and (e) elastase inhibitor at concentration lower than the concentration that completely abrogates necrosis reduces necrotic cell death and partially shifts necrotic cell death to apoptotic cell death (see Figure 10B as compared to Figure 10A) and paragraphs[0082]-[0083].

These surprising and unexpected results provide evidence for the first time that irreversible and unregulated necrosis of living tissue and cells is significantly inhibited by elastase inhibitors and/or shifted into apoptosis, and thus open the doors to therapeutic prevention of extensive and irreversible tissue damage caused by necrosis. No prior art disclose or suggest a method to abrogate necrosis and shift necrotic cell death into natural apoptotic cell death. Accordingly, the invention is novel and non-obvious over the prior art.

5. There is no Reason to Combine the Elements in the Fashion Claimed

The Office Action, at page 17, contends that "*It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. amounts of the agents), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation.*" Such an allegation, however, is improper because no prior art discloses that elastase inhibiting agents inhibit necrosis and partially shift necrosis to apoptosis, and the present invention is certainly not limited to the determination of optimal amounts of different variables in a composition. As demonstrated above, the discovery that different elastase inhibiting agents, i.e., a peptidic inhibitor, elastase inhibitor III, and a heterocyclic inhibitor, abrogate necrosis is novel and unobvious. Accordingly, deducing the amount of elastase inhibiting agent required to inhibit necrosis and cause the partial conversion of necrosis to apoptosis is not a trivial matter, as the Examiner improperly alleges, but requires extraordinary skills. As clearly demonstrated, nothing in the combination of Gyorkos and Rohn would lead the artisan skilled in the art to construe the claimed invention. Thus, the Office's allegation of obviousness is impermissible.

For at least all the reasons stated above, the rejection of claims 1, 3, 18 and 21 under 35 U.S.C. § 103(a) is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, Applicants assert that the pending claims are allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

/ Liliana Di Nola-Baron /

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